Gyrase-DNA Complexes Visualized as Looped Structures by Electron Microscopy*

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Gyrase bound to duplex DNA in the absence of ATP is seen by electron microscopy as a nearly spherical particle frequently located at the intersection of two duplex DNA strands. Such looped structures with gyrase situated at the base of the loops are observed with both linear and circular DNA substrates, and two or three individual DNA molecules bound to the same molecules found at DNA intersections. Looped structures similar to those of the gyrase-DNA complex are also observed with the complex of DNA and the A subunit of gyrase. When negatively supercoiled DNA which has been partially relaxed by gyrase in the absence of ATP is fixed for electron microscopic examination, intermediate forms are observed that contain both supercoiled and relaxed loops in a single DNA molecule, with the enzyme located at the common base of the loops. These results suggest that gyrase possesses multiple DNA-binding sites, a feature which allows the enzyme to hold DNA in constrained loops. The relation of these observations to the mechanism of gyrase action is discussed.

The type II DNA topoisomerases are ubiquitous enzymes characterized by their catalysis of double-stranded breakage and rejoicing of DNA and the passage of a second duplex DNA segment through the transiently broken DNA (for reviews, see Refs. 1-3). The most extensively studied member of this group, bacterial DNA gyrase, has been implicated in a wide spectrum of cellular processes, notably in replication and transcription. In vitro as well as in vivo, gyrase catalyzes the negative supercoiling of DNA in an ATP-dependent fashion (4, 5). The enzyme is also known to convert duplex DNA rings into catenanes and vice versa (6) and to unknot duplex DNA rings containing topological knots (7, 8). In the absence of ATP, gyrase can also relax negatively but not positively supercoiled DNA, although only sluggishly (5, 9-11). All these reactions, supercoiling, catenation/decatenation, unknotting, and relaxation, are most likely different manifestations of the same mechanism involving transport of one double strand of DNA through a break in another double strand.

Although much progress has been made in the characterization of the gyrase-catalyzed reactions and in the biochemical analysis of the nature of the complex between DNA and DNA gyrase (12-15), little is known about this strand passage event. Because of the large size of the gyrase molecule, electron microscopy should present one avenue for probing the molecular details of these gyrase-catalyzed reactions. In this communication, we describe our examination of the complex between DNA and DNA gyrase by this technique.

MATERIALS AND METHODS

Preparation of Gyrase-DNA Complexes—DNA gyrase and the A subunit from Micrococcus luteus were prepared as previously described (14). For binding studies, protein-DNA complexes were formed by incubation of gyrase (0.66 \( \mu \)g/ml) or gyrase A subunit (1.1 \( \mu \)g/ml) with DNA (1 \( \mu \)g/ml) at 30 °C for 10 min in a reaction mixture containing 35 mM Tri-HCl, pH 7.5, 20 mM KCl, 20 mM MgCl₂, 0.1 mM EDTA, 10 mM \( \beta \)-mercaptoethanol, 1 mM spermidine, and 10% glycerol. In some cases, the imido analog of ATP (\( \beta,\gamma \)-imido-ATP) was then added to 0.5 mM, and the incubation continued for another 5 min at 30 °C. For supercoiling reactions, ATP was added to 1 mM. DNA was either relaxed, covalently closed pBR322 DNA or plasmid pMC1 DNA, or plasmid pBR322 DNA linearized with EcoRI endonuclease. The gyrase holoenzyme and the A subunit were stored at -20 °C as a stock solution of 1.1 mg/ml and diluted 10- to 20-fold immediately before use into 10% glycerol, 10 mM \( \beta \)-mercaptoethanol. The activity of the gyrase enzyme was monitored by agarose gel electrophoresis of relaxed DNA as described previously (14). The gyrase-DNA core particles were formed by digestion with staphylococcal nuclease as described by Klevan and Wang (14).

For relaxation of supercoiled DNA, gyrase (an approximately 4:1 molar ratio of gyrase to DNA) was incubated at 37 °C with 8 \( \mu \)g/ml supercoiled pBR322 DNA or PFF2 DNA (an 11-kilobase pair plasmid derived from pBR322, and kindly provided by Steven Hardies, University of North Carolina) in a buffer of 35 mM Tris-HCl, pH 7.5, 20 mM KCl, 20 mM MgCl₂, 0.1 mM EDTA, 10 mM \( \beta \)-mercaptoethanol, 2 mM spermidine, 10% glycerol. Gyrase was added to a final concentration of 1 mg/ml, and the incubation proceeded for 10 min at the indicated temperature, and then after chilling on ice, incubation was continued for another 30 min. For gyrase-DNA core particles, the same two-step fixation procedure was used, but at 0 °C. Samples were then diluted 5- to 10-fold with 160 mM NaCl, 20 mM sodium phosphate, pH 7.5, 1 mM EDTA, mounted onto glow-charged carbon films using a spermidine buffer, and rotary shadowed with tungsten (16). Complexes with the 11-kilobase plasmid were visualized by the cytochrome c drop-spread- ing technique (17).

Electron Microscopy—Complexes of DNA and gyrase or the gyrase A subunit were fixed by the addition of formaldehyde to a final concentration of 1% and sodium phosphate, pH 7.5, to 30 mM for 10 min at the incubation temperature, and then after chilling on ice, glutaraldehyde was added at a concentration of 0.5% for another 10 min. For gyrase-DNA core particles, the same twostep fixation procedure was used, but at 0 °C. Samples were then diluted 5- to 10-fold with 160 mM NaCl, 20 mM sodium phosphate, pH 7.5, 1 mM EDTA, mounted onto glow-charged carbon films using a spermidine buffer, and rotary shadowed with tungsten (16). Complexes with the 11-kilobase plasmid were visualized by the cytochrome c drop-spread- ing technique (17).

Density Banding—In these experiments, the concentrations of relaxed \( ^{3} \)H-labeled pBR322 DNA and gyrase (or gyrase A subunit) were increased to 80 and 10 \( \mu \)g/ml, respectively. Otherwise the incubation and fixation conditions were identical with those described for gyrase binding. Fixed samples (50-100 \( \mu \)l) were layered onto 3.5 ml of...
a CoCl solution with a density of 1.605 to 1.608 g/ml, and centrifuged 17 h at 47,000 rpm, 25 °C, in a Sorvall TV865 vertical rotor. Fractions containing nucleic acid were either desalted by passage over Sepha-
rose 4B and directly prepared for electron microscopy by the sper-
midine-mounting technique, or first diluted 5-fold and deproteinized by the addition of proteinase K to 50 μg/ml for 60 min, 56 °C, phenol-
extracted, ethanol-precipitated, and after resuspension, spread by the cytochrome c drop technique (17).

RESULTS

Visualization of the Gyrase-DNA Complex—It is known that DNA gyrase forms a stable complex with DNA that can be trapped on nitrocellulose or glass fiber filters (13, 18, 19). Digestion of the complex with staphylococcal nuclease yields a core particle that contains two each of the A and B gyrase subunits and a DNA segment about 150 base pairs in length (14). There is strong evidence that the bulk of this DNA segment is wrapped outside the enzyme (12, 13, 20, 21).

Fig. 1 is an electron micrograph depicting a field of the staphylococcal nuclease-digested gyrase-DNA core particles after fixation with formaldehyde and glutaraldehyde and ro-
tary shadowing with tungsten. These core particles have a spherical appearance with an average diameter of 23 ± 5 nm. The weight of the core particles calculated from the weights of its protein and DNA components is 530,000/6.0 × 1010 or 8.7 × 1015 g. From the value of 0.70 cm3/g for the partial specific volume of the core complex (14), the volume of the particle can be estimated to be 6.1 × 1018 cm3, which corre-
sponds to that of a sphere with a diameter of 15 nm. The 23 ± 5 nm average diameter obtained from microscopy appears reasonable due to the flattening of the protein during drying and the increase in diameter by the deposited metal.

The gyrase-DNA complex was also observed when gyrase was bound to undigested plasmid DNA. The enzyme and DNA were incubated at 30 °C in the absence of ATP and under conditions that are optimal for the binding of M. luteus gyrase to DNA (14). The resulting complex was fixed first with formaldehyde at the incubation temperature and again with glutaraldehyde at 0 °C, mounted on thin carbon films, and tungsten-shadowed as described previously (16). Fig. 2 depicts several examples of gyrase molecules bound to DNA. Frames A-D show the association of gyrase with relaxed, covalently closed pBR322 DNA. The 420,000-D gyrase mole-
cule is easily visible as a nearly spherical particle 24 ± 2 nm in diameter. This is close to the size of Escherichia coli RNA polymerase (M r = 470,000) prepared by a similar technique (22).

The circular DNA in the complex is frequently seen as a multiple-looped structure, with the gyrase molecule at the crossover point of the DNA strands. Examination of 100-200 molecules shows that about 74% of the DNA-bound gyrase molecules are at crossovers; 65% of this class had three loops (Fig. 2, c and d), and occasionally structures with four or five loops are seen. The size of the loops varies. Some loops are less than 10% of the total DNA length (Fig. 2d), while in other cases, the loops are similar in size (Fig. 2c). If the fixation is omitted, few DNA-bound particles are visible. If fixation is carried out after first chilling the gyrase-DNA incubation mixture at 0 °C, fewer enzyme molecules (40%) appear at intersections of DNA duplexes, although the number of DNA-bound gyrase remains about the same as before. A similar decrease (39%) in the frequency of gyrase molecules at crosso-
vers of DNA strands was observed when the nonhydrolyzable ATP analog βγ-imido-ATP was added to the gyrase-DNA reaction mixture prior to sample fixation. In this case, the number of complexes containing three loops instead of two loops decreased 3-fold, as compared to the results without the analog. These findings suggest that, while gyrase can hold a DNA duplex in at least two places, the attachment sites may not be equivalent.

When pBR322 DNA linearized by cutting with the restric-
tion endonuclease EcoRI was used in place of the circular form, looped structures are again observed (Fig. 2, e-g). While the fraction of gyrase found at DNA intersections is signifi-
cantly lowered, to about 46%, this observation does show that circular genomes were not a prerequisite for loop formation. Structures in which two linear DNA molecules braid to a single gyrase particle are also seen (Fig. 2h). Plotting of the positions of gyrase on the linear DNA gives a broad histogram lacking distinct peaks.

The similarity in size between gyrase particles found at intersections of DNA strands and nucleic-acid-derived core particles which contain a single gyrase A2B2 holoenzyme indicated that one gyrase tetramer is probably sufficient to hold two duplex DNA strands together. This suggestion was confirmed by electron microscopic examination of gyrase-DNA com-

![Fig. 1. Gyrase-DNA core particles prepared by staphylococcal nuclease digestion.](image-url) Samples were fixed with formaldehyde and glutaraldehyde, mounted on carbon-coated grids, and tungsten-shadowed. Bar = 200 nm.

![Fig. 2. Visualization of M. luteus gyrase on circular and linear DNA.](image-url) Gyrase (0.66 μg/ml) and DNA (1 μg/ml) were incubated at 30 °C for 10 min, fixed with formaldehyde and glutaraldehyde, mounted on carbon-coated grids, and tungsten-shadowed. The molar ratio of gyrase tetramer to DNA in the reaction mixture was approximately 4:1, but in general, only one particle was observed on each DNA molecule. a-d, gyrase on relaxed, covalently closed pBR322 DNA. e-h, gyrase bound to pBR322 DNA cut with EcoRI restriction endonuclease.
plexes which had been separated from free DNA by sedimentation in a shallow CsCl gradient. Equinolar complexes of gyrase and relaxed [3H]thymidine-labeled pBR322 DNA were prepared and fixed as described previously. The incubation mixture was layered onto a CsCl solution and centrifuged for 17 h in a vertical rotor. The position of the radioactively labeled DNA is shown in Fig. 3A. This gradient gave a sharp peak of free DNA (fractions 2-7) and a broad peak of a lighter density (fractions 11-21). By electron microscopy, most of the complexes in this latter region contained two to three monomeric pBR322 DNA molecules and one or more particles of bound protein (Fig. 3B). To test whether these structures contained multimeric pBR322 DNA or separate monomeric DNA rings held together by gyrase, the samples were deproteinized and again examined by electron microscopy. 95% of the DNA was released as monomer-length circles. Thus, under these conditions, the DNA concentration is high enough that gyrase can interact with multiple DNA molecules rather than with multiple sites on a single DNA molecule.

If the buoyant density of DNA in cesium chloride is taken as 1.7 g/ml and that of protein as 1.3 g/ml (23), the binding of a tetrameric gyrase to a pBR322 DNA molecule is expected to reduce the buoyant density of the DNA by about 50 mg/ml (14). In the gradient of Fig. 3A, no label was detected at the density expected for 2 gyrase molecules/DNA genome. Instead it appears that the complexes banded near the values predicted for 1 gyrase/2 DNA molecules, 2 gyrase/3 DNA molecules, and 1 gyrase/1 DNA molecule, in order of decreasing density. Some complexes showed the distinction between one and two gyrase molecules clearly, as illustrated in Fig. 3B. Multiple gyrase enzymes in the same complex were generally found in close association with each other. While these strong protein interactions do occur, it is evident that one gyrase alone can bind at least two separate duplex DNA strands. Occasionally, as in Fig. 3C, the path of these DNA strands could be determined as they passed over the surface of the gyrase.

**Visualization of Gyrase-DNA Complexes during the Course of DNA Supercoiling and Relaxation**—When relaxed pBR322 DNA is incubated with gyrase in the presence of ATP at 25 °C (before the protein-DNA complex is fixed for electron microscopy), even at short incubation times (3 min), the only visible products of the reaction are tightly supercoiled molecules, often with gyrase bound to them, or relaxed, usu-
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FIG. 5. Complexes observed during the relaxation of negatively supercoiled DNA by gyrase. Gyrase (6 μg/ml) was incubated at 37 °C with negatively supercoiled pBR322 DNA (8 μg/ml). After 60 min, the reaction was interrupted by the addition of formaldehyde at 37 °C, then glutaraldehyde at 0 °C, and the samples were further processed for electron microscopy. a, gyrase bound to supercoiled multiple-looped circles (Fig. 4). The latter probably represent complexes of inactive gyrase molecules or nicked DNA substrate.

Since the ATP-independent relaxation of negatively supercoiled DNA by gyrase is a slower process than the ATP-dependent supercoiling reaction (9, 10, 24), complexes representing intermediate stages of this reaction are more readily trapped. Exemplary molecules sampled during the course of such a reaction are shown in Fig. 5. Under the reaction conditions specified in Fig. 5, DNA molecules sampled at incubation times of 30 min or less appear supercoiled, and gyrase molecules are frequently associated with the supercoiled DNA. By 60 min, both supercoiled molecules and relaxed forms are observed (Fig. 5, a and c) and 10-20% of the DNA-enzyme complexes exhibit intermediate superhelical density. The latter consists mostly of DNA molecules held into loops that are relaxed to different degrees, from tightly supercoiled to completely relaxed (Fig. 5b). Since these structures are not seen at shorter reaction times and the samples were prepared identically, it is unlikely that the relaxed loops were formed by nicking during sample preparation for microscopy. It is not certain how these relaxed loops are created.

When a larger 11-kilobase pair plasmid was used as the substrate for gyrase, a similar progression is also apparent, with supercoiled, partially relaxed, and relaxed forms often present in the same field (Fig. 6). With this larger DNA, two separate gyrase molecules on a single DNA molecule are frequently seen (the relaxed circle R in Fig. 6, for example).

Binding of Gyrase A Subunit to Duplex DNA—It is generally believed that the DNA cleavage and rejoining site of gyrase is located on the A subunit and the ATPase site is on the B subunit, although both subunits must be present for either of these activities (for reviews, see Refs. 1-3). When gyrase-induced cleavage of duplex DNA occurs, the A subunit of the enzyme is found linked covalently to each of the 5'-phosphoryl ends of the broken DNA (25, 26). Covalent closure of a nicked DNA in the presence of gyrase A subunit alone gives a product with a linking number higher than the same DNA sealed in the absence of the protein, and it has been suggested that DNA may form a complex with subunit A in which the DNA is coiled around the protein, similar to the coiling of DNA around the tetrameric gyrase holoenzyme (10). On the other hand, filter binding experiments failed to detect a stable complex, and the possibility of attributing the results described above to the presence of contaminating B subunit was raised (19).

When the gyrase A subunit alone was added to relaxed pBR322 or PM2 DNA under the same conditions used for the holoenzyme binding experiments and fixed for electron microscopy, 16 ± 3-nm diameter particles were observed on the DNA (Fig. 7A). Most of these particles (65%) were at crossover points, and when higher DNA concentrations were used, it appeared that the A subunits could cross-link individual DNA molecules to each other in a manner similar to the gyrase holoenzyme. Thus, the binding of the A subunit to DNA does occur. Since the gyrase A subunit protein exists in solution as dimers (11, 14) and can associate into tetramers in the presence of spermidine (14), it is probably binding in a multimeric form. When analyzed by CsCl density banding (Fig. 7B), these complexes were found at the density predicted for 2 gyrase A protomers/DNA genome. While the B subunit alone has not been examined, these findings suggest that at least the A subunit contributes to the DNA binding activity of the holoenzyme.

DNA at the initial stage of reaction. b, gyrase bound to partially relaxed DNA, resulting in loops with different degrees of superhelicity. c, gyrase bound to relaxed circular DNA. Bar = 100 nm.
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**FIG. 6.** Relaxation of an 11-kilobase pair plasmid by gyrase exhibits a progression from highly supercoiled (S), to partially relaxed (P), to fully relaxed (R) circles. These DNA molecules, prepared by the cytochrome c-spreading technique, are derived from a single micrograph taken at $\times 10,000$ magnification. Bar = 200 nm.

**FIG. 7.** Binding of gyrase A subunit to duplex DNA. A, electron microscopy. Gyrase subunit A (1.1 pg/ml) was mixed with relaxed PM2 DNA (1 pg/ml), incubated at 30°C for 10 min, and prepared as described in Fig. 2. Bar = 200 nm. B, separation of gyrase A-DNA complexes by CsCl density banding. The gyrase A subunit (10 pg/ml) was incubated with [3H]thymidine-labeled relaxed pBR322 DNA (80 pg/ml) at 30°C for 10 min. The complexes were fixed, layered onto a CsCl solution of 1.608 g/ml, and centrifuged 17 h in a vertical rotor. The predicted positions of complexes composed of one, two, or three gyrase A protomers per DNA genome are marked by arrows.

**DISCUSSION**

The electron microscopic findings reported here provide additional support that the gyrase-DNA core complex obtained after staphylococcal nuclease digestion is in the form of a globular particle (14). Furthermore, the size and shape of the gyrase molecule bound to undigested DNA are not very different from those of the core complex. Our results also suggest that the organization of the duplex DNA around the gyrase holoenzyme is primarily determined by its interactions with the A protomers, since the binding of the gyrase A subunit to DNA exhibits characteristics that resemble those of the holoenzyme.

One interesting feature of the gyrase-DNA complex observed by electron microscopy is the high frequency of gyrase molecules found at intersections of DNA duplexes. Although the possibility that the multilooped structures seen are artifacts of the fixation procedures cannot be ruled out, we believe that this is rather unlikely. Such looped structures are rarely seen with most DNA-protein complexes, such as those of *E. coli* RNA polymerase, *E. coli* DNA polymerase, histones, or SV40 large T antigen (16) prepared by fixation procedures similar to the one used here, but have been observed in complexes of DNA and enzymes which might have mechanisms similar to that of gyrase, such as the *E. coli* K restriction enzyme (27), T$_4$ phage topoisomerase, and the φX-174 replication complex.¹

There are several plausible interpretations to account for the location of a gyrase molecule at a DNA intersection. There is substantial evidence that complex formation between gyrase and DNA involves the wrapping of a 150-bp² DNA segment around the enzyme and that the site of enzyme-catalyzed breakage and rejoining of duplex DNA is near the center of this segment (12, 13, 20, 21). It is generally accepted that the action of a type II DNA topoisomerase such as gyrase involves the passage of a duplex DNA segment through the transiently opened DNA gate (6-8, 28). There is little information, however, about the mechanics of strand passage. In the simple "sign-inversion" model for gyrase, the local sense of supercoiling of DNA, which may be determined for example by the coiling of the 150-bp segment of the DNA around the enzyme, is inverted by the crossing of one enzyme-bound DNA duplex segment through another (28). In a more elaborate model, the sense of coiling of the 150-bp DNA segment around gyrase does not change during the cycle of events catalyzed by the enzyme, and strand passage coupled to ATP utilization involves the transport of a second DNA loop through the DNA gate on the 150-bp segment (29). The looped structures observed by electron microscopy support the view that the

¹ J. D. Griffith, unpublished results.

² The abbreviation used is: bp, base pair.
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segment to be transported can be far from the 150-bp segment tightly bound to the enzyme, and can in fact be on a separate DNA molecule, as demonstrated by photographs showing the binding of two or more circular or linear DNA molecules to gyrase. The separation of the segment to be transported from the 150-bp loop is also consistent with the catenation and unknotting reactions that are known to be catalyzed by gyrase (6–8).

Another interesting point raised by the electron microscopy results is the direction of transport of the DNA segment. The type of models discussed in Wang et al. (29) specifies two states of the segment to be transported: an outside state in which the segment resides outside the gyrase DNA core complex and an inside state in which the segment resides inside the enzyme and the 150-bp loop. The direction of transport across the DNA gate can be specified only if the sense of wrapping of the 150-bp segment around gyrase is known. If the wrapping is right-handed, a reduction of the linking number requires the transport from outside to inside. In this case, the coupling of transport to ATP utilization in turn requires that the outside state is the favorable one in the absence of ATP, and that ATP binding shifts the equilibrium toward the inside state. On the other hand, if the wrapping is left-handed, the opposite will be the case: a reduction of the linking number requires the transport across the DNA gate to be from inside to outside, and the inside state is the favorable one in the absence of ATP (29).

The finding here that gyrase molecules are located preferentially at intersections of DNA duplexes could be attributed to the dominance of the inside state when ATP is not bound to the enzyme, which would in turn specify a left-handed wrapping of the 150-bp DNA segment around gyrase. The apparent reduction of gyrase molecules found at DNA crossovers by the addition of the nonhydrolyzable $\beta$,y-imido analog of ATP is entirely consistent with this interpretation, since the binding of this compound would be expected to shift the equilibrium toward the outside state.

Alternatively, the looped structures seen in the electron micrographs may also reflect the presence of external DNA-binding sites on gyrase in addition to those involved in the binding of the 150-bp DNA segment. These additional DNA-binding sites may serve the purpose of bringing the DNA segment to be transported to the proximity of the DNA gate. In this case, ATP analog binding would cause the segment to be transported through both the 150-bp loop and the enzyme and then expelled. Hydrolysis of ATP would be required before binding of the transported segment could reoccur. It is also plausible that the 150-bp segment which interacts with gyrase is not a contiguous segment and may contain a loop. If this is true, exonuclease digestion of the DNA·gyrase complex may reveal nucleic-resistant segments much longer than 150 bp because of the presence of internal loops. These longer nucleic-resistant segments are expected to be heterogeneous in size, however, and would have escaped detection in previous studies with exonucleases (12, 21).

An interesting and puzzling feature of the multilooped gyrase·DNA structures visualized by electron microscopy is the simultaneous presence of supercoiled and relaxed DNA loops in a single supercoiled DNA molecule that has been partially relaxed by gyrase (Fig. 5). Although gyrase models that were proposed prior to the realization of DNA duplex breakage and passage predicted the separation of supercoiled and relaxed regions (10, 30), the more recent models incorporating duplex breakage and passage do not (7, 8, 18, 28, 29). The existence of supercoiled and relaxed loops in a partially relaxed DNA molecule suggests that a supercoiled loop in the multiloop gyrase·DNA complex can remain intact while the other loops are relaxed. A gyrase molecule may be able to constrain this loop by binding to at least two sites at the base of the loop.

Liu et al. (7) have previously postulated the initiation of phase T, DNA replication by a localized supercoiling action of the ATP-dependent phase T, DNA topoisomerase at the origin of replication. This hypothesis, as well as broader ones regarding the modulation of genetic processes by localized DNA supercoiling and relaxation, remains to be tested experimentally. The electron microscopy evidence presented here, that a topoisomerase might be able to relax or supercoil a part of a long DNA molecule by holding that part in a constrained loop, adds further impetus for studying the possibility of localized supercoiling and relaxation, and the biological effects of such events.

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